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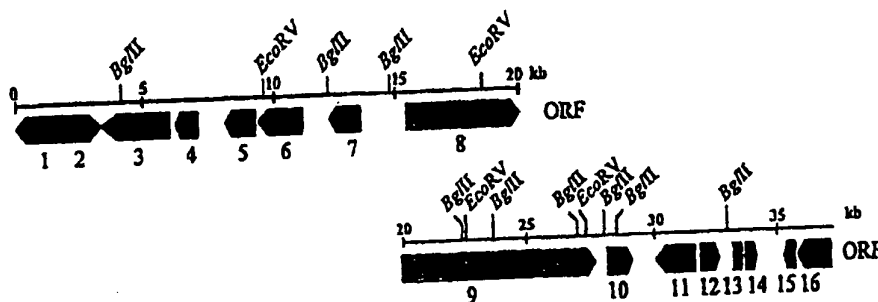
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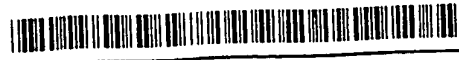
[Continued on next page]

(54) Title: DNA SEQUENCES FOR ENZYMATIC SYNTHESIS OF POLYKETIDE OR HETEROPOLYKETIDE COMPOUNDS



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(57) Abstract: The invention consists of: (1) cloned *Sorangium cellulosum* polyketide synthase (PKS) biosynthetic cluster DNA; and (2) the nucleotide sequence and predicted protein coding sequences of the cloned DNA. The invention can be used for, but not limited to: (a) increasing yields of PKS product in *Sorangium cellulosum* (e.g., by amplification or genetic modification of the epothilone gene cluster or its component parts); (b) increasing yields of polyketide product in a heterologous system by transfer of the epothilone gene cluster or its component parts, which may be followed by amplification or genetic modification of the PKS gene cluster or its component parts; (c) modification of the polyketide product chemical structure in either *Sorangium cellulosum* or a heterologous host (e.g., by genetic modification of the epothilone gene cluster or its component parts); and (d) for the detection of genes and gene products involved in making polyketides or related molecules in other organisms (e.g., by hybridization or complementation assays). DNA sequence and analysis is presented for the following cosmids and plasmids: A2 cosmid; the pEPOcos6 region (overlapping of pEPOcos6 and pEPOcos7); pEPOcos8 cosmid; A5 cosmid; Sau4 (10 kb plasmid).



(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/23535

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/52 C12N9/00 C12N15/63 C12N5/10 C12P17/06
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	US 5 716 849 A (SCHUPP THOMAS ET AL) 10 February 1998 (1998-02-10) abstract column 1, line 15 - line 23 column 4, line 8 - line 33 column 4, line 66 - column 5, line 40 example 1 --- -/--	1,3-5, 16,17, 22,23 18-21

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

18 August 2000

Date of mailing of the international search report

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Name and mailing address of the ISA
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CEDER O.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/23535

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHUPP T ET AL: "SORANGIUM CELLULOSUM (MYXOBACTERIUM) GENE CLUSTER FOR THE BIOSYNTHESIS OF THE MACROLIDE ANTIBIOTIC SORAPHEN A: CLONING, CHARACTERIZATION, AND HOMOLOGY TO POLYKETIDE SYNTHASE GENES FROM ACTINOMYCETES" JOURNAL OF BACTERIOLOGY, vol. 177, no. 13, July 1995 (1995-07), pages 3673-3679, XP000893003 WASHINGTON, DC ISSN: 0021-9193 the whole document	1,3-5, 16,17, 22,23
X	WO 93 13663 A (ABBOTT LAB) 22 July 1993 (1993-07-22) abstract	1,16,17, 21,23
A	WO 98 22461 A (BIOTECHNOLOG FORSCHUNG GMBH ;GERTH KLAUS (DE); HOEFLE GERHARD (DE)) 28 May 1998 (1998-05-28) the whole document	2,24
P,X	BEYER S ET AL: "METABOLIC DIVERSITY IN MYXOBACTERIA: IDENTIFICATION OF THE MYXALAMID AND THE STIGMATELLIN BIOSYNTHETIC GENE CLUSTER OF STIGMATELLA AURANTIACA SG A15 AND A COMBINED POLYKETIDE(POLY)PEPTIDE GENE CLUSTER FROM THE EPOTHILONE PRODUCING STRAIN SORANGIUM CELLULOSUM SO CE90" BIOCHIMICA ET BIOPHYSICA ACTA. GENE STRUCTURE AND EXPRESSION, vol. 1445, no. 2, 14 May 1999 (1999-05-14), pages 185-195, XP000915670 AMSTERDAM ISSN: 0167-4781 the whole document	1-5
E	WO 99 66028 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); SCHUPP THOMAS (CH)) 23 December 1999 (1999-12-23) the whole document	1-6,8, 16-24
E	WO 00 31247 A (KOSAN BIOSCIENCES INC) 2 June 2000 (2000-06-02) the whole document	1-6,8, 16-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/23535

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-5 and 16-24 partly and 6,8 completely

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-5 and 16-24 partly and 6,8 completely

Nucleic acid and polypeptide sequences involved in polyketide synthesis and related to cosmid A2 and their uses, where the sequences are seq id nos 1,3-34.

2. Claims: 1-5 and 16-24 partly and 7,9 completely

Nucleic acid and polypeptide sequences involved in polyketide synthesis and related to the pEPOcos6 region and their uses, where the sequences are seq id nos 2,35-70.

3. Claims: 1-5 and 16-24 partly and 10,11 completely

Nucleic acid and polypeptide sequences involved in polyketide synthesis and related to the pEPOcos8 region and their uses, where the sequences are seq id nos 71-88.

4. Claims: 1-5 and 16-24 partly and 12,13 completely

Nucleic acid and polypeptide sequences involved in polyketide synthesis and related to the cosmid A5 and their uses, where the sequences are seq id nos 89-118.

5. Claims: 1-5 and 16-24 partly and 14,15 completely

Nucleic acid and polypeptide sequences involved in polyketide synthesis and related to plasmid Sau4 and their uses, where the sequences are seq id nos 119-123.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/23535

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